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Establishing the Evidence Bar for Molecular Diagnostics in Personalised Cancer Care

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Key Words

Biomarkers · Molecular diagnostics · Validation · Clinical utility · Personalised medicine · Companion diagnostic · Policy · Regulatory requirements

Abstract

While personalised cancer medicine holds great promise, targeting therapies to the biological characteristics of patients is limited by the number of validated biomarkers currently available. The implementation of biomarkers has undergone many challenges with few biomarkers reaching cancer patients in the clinic. There have been many biomarkers that have been published and claimed to be therapeutically useful, but few become part of the clinical decision-making process due to technical, validation and market access issues. To reduce this attrition rate, there is a significant need for policy makers and reimbursement agencies to define specific evidence requirements for the introduction of biomarkers into clinical practice. Once these requirements are more clearly defined, in an analogous manner to phar-

maceuticals, researchers and diagnostic companies can better focus their biomarker research and development on meeting these specific requirements, which should lead to the more rapid introduction of new molecular oncology tests for patient benefit.

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Introduction

The four most common cancer sites in Europe are breast, colorectal, prostate and lung cancers which comprise approximately 1.7 million cancers diagnosed or about half the incidence of cancer [1]. Many cancer therapeutics have been or are being developed in these malignancies and their subtypes. The European Medicines Agency (EMA) has approved 48 drugs since 1995 which address indications in one or more of these cancer diseases; however, only 18 of these therapies are correlated with companion diagnostics (CDxs), based on the use of 5 biomarkers [2]. Currently, the traditional 'one size fits

all' development of cancer agents leads only to statistically significant but marginal clinical benefit; so, employing biomarkers to better select patients for therapies underpins the personalised or precision medicine approach to identify reliably those patients who will derive benefit from treatment. In 2014, there were approximately 800 cancer agents in phase II or III clinical trials in the United States [3]; many of these drugs are intended to target specific biological pathways; validated biomarkers are required to identify those tumours in which these drugs are likely to be active. Therefore, there is an urgent need to develop a system which is more efficient in introducing biomarkers into clinical practice. Currently, there are less than 20 prognostic or predictive biomarkers which are recognised in the 2014 European Society of Medical Oncology (ESMO) clinical practice guidelines for lung, breast, colon and prostate as having sufficient evidence to be recommended for clinical practice [4–8]. In prostate cancer, there are a number of prognostic biomarkers available to guide clinical management of disease, but there are no established predictive biomarkers to choose one particular treatment. There have been thousands of studies published in the scientific literature claiming cancer biomarkers are clinically useful, but these biomarkers hardly ever reach clinical application for a wide variety of reasons [9]. Most of the issues relate to analytical and clinical validation, demonstration of clinical utility, regulatory approval, health technology assessment, reimbursement and adoption in clinical practice [10].

Valuing Biomarkers or Molecular Diagnostics on a Par with Therapeutics

Imatinib mesylate is often cited as the first targeted therapy, approved in 2001, as it was effective for patients with chronic myelogenous leukaemia who were selected for treatment based on the presence of a cytogenetic biomarker. Patients who responded to this therapy had an acquired genetic aberration in their tumour cells known as the Philadelphia chromosome and/or the BCR-ABL gene [11]. This targeted therapy and biomarker combination improved survival in patients with this disease. In an analysis of >3,000 patients diagnosed with chronic myelogenous leukaemia in the Swedish Cancer Registry between January 1, 1973, and December 31, 2008, survival increased significantly after 2001 for patients up to 79 years of age [12]. Overall, 5-year relative survival rates were 0.21 in the calendar periods 1973 to 1979 compared to 0.80 for patients between 2001 and 2008. The value of

imatinib mesylate was understood when it was combined with a biomarker which identified which patients would benefit from this therapeutic intervention.

As personalised medicine is in its infancy, one of the current challenges with the initial class of CDxs is that they were developed to predict response to a particular drug in low-frequency populations, which is unlikely to lead to a cost-effective strategy if many patients need to be tested to identify those likely to benefit. An example of this is crizotinib, which is an effective treatment for patients with an ALK aberration in metastatic non-small cell lung cancer (NSCLC). If EML4-ALK fusion testing was performed on all stage IV non-squamous NSCLC patients, <5% of the population would be identified for crizotinib treatment [13]. Therefore, in this scenario, one would have to order 20 tests to identify 1 patient who may benefit from the therapy; so, from the perspective of the healthcare system, they have to pay for 20 tests and 1 course of therapy to find the 1 patient with ALK aberration who may benefit from crizotinib [14, 15].

Therefore, an emerging option may be to consider molecular diagnostics in a different way – rather than focusing on a one-to-one relationship between biomarkers and therapeutic intervention, consider the development of biomarker panels or platforms which would inform decisions on multiple drugs and treatment options. Using this approach would then permit the development of robust algorithms to support clinical decision making. This platform type approach would allow the value associated with testing to be attributed to a wider range of treatment options and an increase in the number of validated biomarkers on the panel would increase the value of the panel [16]. This concept is similar to Metcalfe's law, which is often used to describe the value of the Internet or social media, where an increase in the number of users increases the value of the service to the overall community. Therefore, these initial tests should be considered like the first Internet users where the costs are higher and the value will only be realised once the number of validated biomarkers expands and can be tested on a common platform. While the tests may be able to run on a common platform, there will still be cost to validate each biomarker independently with each drug for each patient population. Ultimately, supporting access to value-based molecular diagnostics will lead to more investment in new biomarkers designed to increase the effectiveness of cancer drugs. The initial application of a biomarker platform in clinical practice is most relevant in NSCLC, as seen in table 1, since there are the most approved targeted therapies for these tumours.

Table 1. Currently available CDxs in breast, colorectal, lung and prostate cancers

Year	Therapeutic area	Medicine name	Common name	CDx
1996	breast	Fareston	toremifene	ER
1996	lung	Hycamtin	topotecan	EGFR
2000	breast	Herceptin	trastuzumab	HER2+
2000	breast	Arimidex	anastrozole	ER
2001	breast	Femara	letrozole	ER
2004	colorectal	Erbitux	cetuximab	RAS WT
2004	breast	Faslodex	fulvestrant	ER
2005	lung	Tarceva	erlotinib	EGFR
2005	breast	Aromasin	exemestane	ER
2007	colorectal	Vectibix	panitumumab	RAS WT
2008	breast	Tyverb	lapatinib	HER2+
2009	breast	Afinitor	everolimus	HR+, HER2-neg
2009	lung	Iressa	gefitinib	EGFR
2012	lung	Xalkori	crizotinib	ALK
2013	lung	Giotrif	afatinib	EGFR
2013	breast	Kadcyla	trastuzumab emtansine	HER2+
2013	breast	Perjeta	pertuzumab	HER2+
2015	lung	Zykadia	ceritinib	ALK

What Is the Ideal Biomarker?

The ideal biomarker is one that supports clinical decisions by defining a particular biological characteristic of a particular patient. For example, an ideal predictive biomarker for a therapeutic intervention would be binary test which would identify 100% of the candidates who will respond to the therapy and none of the non-responders with appropriate levels of sensitivity and specificity. Comprehensive evidence would have been generated for analytical, clinical validity, clinical utility and cost-effectiveness of this biomarker, allowing the patient, physician and healthcare system to use the biomarker-drug combination with a high level of confidence. This degree of rigour allows all stakeholders to be confident that (a) the test is relevant to address the specific clinical question and (b) the test will be performed accurately, precisely and reproducibly and that the strength of the correlation between biomarker and use of the drug is high.

Thus far, we have considered biomarkers in the context of identifying which patients will respond to a particular therapy. Additional biomarkers may also be relevant for assessing toxicity, deciding dosing schedule or measuring response to therapy. For example, the current gold standard for assessing a patient's response to imatinib mesylate involves the use of a real-time quantitative

PCR assay that measures BCR-ABL transcripts (a BCR ABL/ABL ratio). A three-log reduction in BCR-ABL/ABL ratio within a specific time after therapy equates with a molecular response to imatinib mesylate treatment. Other biomarkers that may be relevant include those which assess risk/benefits of particular treatment options. In all of these scenarios, appropriate clinical research should inform the evidence for the application of a biomarker in a particular clinical setting.

Validation of Molecular Diagnostics or Biomarkers

Many high-quality guidelines have been published which clearly outline the standards required for validating biomarkers [17–25]. The gold standard for predictive biomarkers still relies on randomised controlled clinical trials. However, validating biomarkers in prospective randomised controlled clinical trials is becoming increasingly costly, especially as many emerging biomarkers are addressing small populations and studies need to recruit patients from multiple countries to identify a sufficient number of patients to report meaningful results. Applying approaches from rare cancers could be considered to a broader set of clinical research where direct randomised trial evidence is considered with a higher level of uncertainty around the results [26]. There is a need to have researchers, regulators and reimbursement agencies to align on clinical trial methodologies that can be used to validate biomarkers knowing that randomised controlled clinical trials are not always feasible. For example, using archival tissue from randomised controlled clinical trials or large registry cohorts can provide relevant information. This approach is being employed by the Stratification in COloRecTal Cancer (S-CORT) consortium to develop and validate new biomarkers in over 2,000 archival patient samples from clinically well-annotated randomised clinical trials and cohort studies [27].

Key Principles in the Validation of Molecular Diagnostics

Most biomarkers can be classified as providing either prognostic or predictive information. A prognostic marker is measured before treatment to indicate the outcome for patients that are untreated (pure prognostic marker) or receive a standard treatment (context-specific prognostic marker). A predictive marker is measured before treatment to identify patients who will or will not benefit from a particular therapy. 'A biomarker is predictive if the treatment effect (experimental compared with control) is

different for biomarker-positive patients compared with biomarker-negative patients', and a 'formal test for an interaction between the biomarker and treatment group is shown to have a significant interaction' [28]. In certain cases, prognostic markers may wrongly be considered to have also a predictive value, especially when they can identify patients who have a very good prognosis, irrespective of therapy. This biomarker, even if it is not strictly speaking 'predictive', still provides valuable information on the likely benefit of that particular therapy in this low-risk group. An example of this is for stage 2 colon cancer patients who are DNA mismatch repair (MMR) deficient; as their prognosis is very good, they are unlikely to benefit from fluorouracil + leucovorin chemotherapy. On the other hand, it would be inappropriate to attribute to this marker a predictive value as a decision made based on MMR status to limit therapeutic intervention in a higher-risk group would lead to undertreatment. Therefore, it is important to consider both the prognostic and predictive information together to understand overall outcome before considering the benefit of a particular therapy.

Relevance of Population for Validation and 'Intended Use of the Biomarker'

When a molecular diagnostic test is developed, it is important that there is a clear intended use for the biomarker in a specific group of patients. One of the challenges with many biomarkers is that even if they provide prognostic or predictive information which are consistently and independently validated (clinical validity), this information is not actionable because the markers are not therapeutically relevant (clinical utility). For example, if you have a test that identifies patients who are likely to recur 6 months earlier than that indicated by currently available methods, but none of the currently available therapies will change the patient's outcome, the information that the biomarker provides does not offer any actionable information for clinicians. Another key issue is the appropriate definition of the patient group for which the biomarker is intended to be used. For example, if one develops a test to identify a group of early-stage cancer patients who are unlikely to benefit from a specific therapy, but the test is validated in a group of patients with very low risk of recurrence based on traditional parameters, it is unlikely that the test will offer much value. This is why biomarkers should be validated in patients with similar characteristics to the patients for which the biomarker is intended for use in the clinical setting.

Analytical Validation

Before any molecular diagnostic is validated to demonstrate its clinical value, it is first important that the assay methods are validated which includes the pre-analytical and the post-analytical steps. Analytical validation is an important first step to confirm that the methods used for the molecular diagnostic is accurate, precise, reproducible, specific and robust in all the settings where the assay may be conducted. Many biomarkers used in clinical practice today have a discordance rate of 10–15% between local and central testing, and there are many reasons for this, including how the specimen is prepared, differences in test protocols and methods, cut-off points and method of reporting [29]. In many countries, the current regulatory requirements are designed to support quality systems and reproducibility of the diagnostic [30].

Clinical Validity

Clinical validity is defined as the ability for a biomarker to accurately and reliably predict the clinically defined disorder or phenotype of interest [31]. It is essential that the methodology used for validation appropriately assesses the clinical value of the assay as an independent factor in addressing the clinical question that the biomarker is intended to address. One of the biggest challenges in validating biomarkers is that there are many sources of bias that can impact a specific result. Therefore, repeated validation in multiple studies with consistent results is a prerequisite before an assay is introduced into clinical practice. Examples of a molecular diagnostics which followed this approach were KRAS and Oncotype DX breast cancer assay.

Besides validating a biomarker in a randomised controlled clinical trial, there are other methodologies which can provide a high level of evidence if conducted in a robust manner based on archived tissue. One of the first examples where this approach was followed by regulatory agencies involved the approval of cetuximab and panitumumab for use in metastatic colorectal cancer patients with wild-type KRAS tumours by the EMA; this decision was made based on KRAS mutational data generated from 4 randomised pivotal trials (2 cetuximab, 2 panitumumab) [32]. The guidelines generated by EMA are increasingly being followed by clinicians, guideline committees and reimbursement agencies to support the use of KRAS testing in this setting. A second example is the Oncotype DX breast cancer assay which was developed in 2003. The assay was defined specifically and was analytically validated before its first clinical validation study was conducted [33]. Following this step, the assay was vali-

Table 2. Validation using archived specimens in evaluation of prognostic and predictive biomarkers

1	There should be sufficient representative samples from the original randomised controlled clinical trial to ensure adequate statistical power
2	The test should be analytically and pre-analytically validated for use with archived tissue
3	There should be a pre-specified protocol and statistical plan for the biomarker evaluation
4	The results from the study should be confirmed in an independent study using archived specimens with a consistent approach

dated in 9 additional studies that were based on archival tissue, the majority of which came from randomised controlled studies [34]. The first results from the TAILORx study, a study which prospectively assigned patients to chemotherapy based on the Oncotype DX score, has recently been published. This study has reported that 99.3% of the patients with low Oncotype DX assay recurrence scores between 0 and 10, treated with endocrine therapy alone, were free of distant recurrence at 5 years [35]. These results are consistent with those results from studies using a prospective retrospective design. Simon et al. [18] proposed four main criteria, listed in table 2, that should be considered for a prospective retrospective design to have a high level of evidence.

Utilising Population-Based Cohorts to Validate Markers with High Level of Evidence

While prospective studies based on archived tissue from randomised controlled clinical trials are increasingly useful to validate biomarkers, there are not randomised clinical trials with archived samples to address every question that biomarkers can help answer. Therefore, there will be a need to develop methodologies and guidelines to use large population-based cohorts to validate biomarkers with a high level of evidence, especially for early-stage disease where long follow-up is needed to demonstrate clinical utility. For example, new prostate cancer genomic tests have been introduced which are developed to identify patients who are candidates for active surveillance based on prostate cancer biopsy, and it is unlikely that archived biopsy tissue samples are available from well-conducted large prospective clinical trials that randomised patients between active surveillance and active treatment (radiation or prostatectomy) [36]. Several

commercially available multiple gene panels such as ProLaris, Oncotype DX Genomic Prostate Score and Decipher have recently become available to estimate disease outcome in different clinical settings that have been validated in population-based studies. These gene panels are currently employed in clinical practice to help decide for active surveillance or treatment with curative intent. Due to the lack of randomised controlled clinical trials with archived tissue, the current assays have been validated retrospectively in large population-based cohorts following validation principles such as having pre-specified protocol and statistical plan.

Clinical Utility

Clinical utility is used to define whether a biomarker will impact treatment decisions and will lead to an improvement in patient outcomes [24, 37]. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) defines the clinical utility of a genetic test as the evidence of improved measurable clinical outcomes and its usefulness and added value to patient management decision-making compared with current management without genetic testing [31]. Patient outcomes can be improved through a decision to either receive a treatment which improves the patient's prognosis, or by avoiding an unnecessary treatment that can impact the patient's quality of life. A biomarker can be considered useful if the results are actionable and lead to a better treatment approach. Clinical utility can often be demonstrated in studies that show that a molecular diagnostic test will modify a treatment approach based on the results of the test. If practice patterns are significantly different in different markets, it is important to establish clinical utility according to local practice. For this reason, some reimbursement and health technology agencies are focused on understanding clinical utility in a real world setting as clinical decisions are multifactorial, and the impact of a test can be most appropriately evaluated relative to other factors. In general, there are disparate assessment approaches regarding the definition and demonstration of clinical utility by different stakeholders in different healthcare systems, so more uniform standards for evidence requirements are needed especially as clinical practice patterns are heterogeneous across countries.

Economic Validation

Cost-effectiveness is used to define whether a specific technology represents good value for money. Cost-effectiveness analyses therefore compare the costs and outcomes of therapeutic alternatives. While economic evalu-

ations of molecular diagnostics are similar to those for therapeutics, there is a need to integrate particular parameters that are specific to diagnostics [38]. The first parameter to capture is the imperfection of the diagnostic test. This usually corresponds to the specificity and sensitivity of the diagnostic test with particular focus on the positive and negative predictive values. The second parameter that needs to be incorporated into the economic analysis is the clinical utility of the diagnostic test (impact of the test on treatment decision making). Molecular diagnostics also provide value to physicians and patients as they increase certainty in treatment decisions. This so called 'value of knowing' is more difficult to quantify and is therefore not often incorporated into the cost-effectiveness analyses.

If cost-effectiveness informs policy makers on whether molecular diagnostics represent good value for money and are therefore worth funding, it does not address affordability questions. This is why budget impact analysis is also normally required by budget holders. Budget impact analyses focus on short-term costs and savings. Knowing that healthcare budgets are limited, the objective of budget impact analyses is to inform budget allocation.

While many healthcare systems tend to focus more heavily on budget impact, cost-effectiveness is the first important question to be addressed. Both analyses should therefore be considered to inform reimbursement and funding decisions. Specific attention must be given to the budget silo issue – it is not uncommon for savings to occur in one budget but for the innovation to be paid for from another. This can lead to situations where the chance of new molecular diagnostic reaching patients becomes even less likely. Innovation funding and savings derived from this molecular diagnostic should therefore come from the same budget.

Pursuing Market Access for Molecular Diagnostic

Introduction of a new molecular test on the market can only occur once it meets all regulatory requirements and it receives reimbursement approval within the healthcare system. Currently, there are a variety of pathways for introduction which depend on the following parameters: (a) the country in which the test is being introduced, (b) whether the molecular test is associated with a therapeutic (CDx), (c) whether it is an in vitro diagnostic test or an imaging biomarker, (d) whether the test is performed locally or in a central lab, and (e) which laboratory discipline performs the test. Each of these factors can influence the evidence and regulatory requirements and which agencies will evaluate the technology.

EU Regulatory Framework

The regulatory system of the EU provides two broad frameworks for approving personalised medicine technologies: one pathway for medical devices and another for in vitro diagnostic devices. Non-in-vitro devices, such as imaging devices, used for cancer screening come under the Regulation on Medical Devices and Amending Directive 2001/83/EC, Regulation (EC) No. 178/2002 and Regulation (EC), whereas most molecular tests (including those classified as CDx) are (and will be) governed by the framework for in vitro diagnostics (IVDs), which encompasses diagnostic products such as reagents, instruments and systems intended for use in diagnosis of disease.

Today's system for IVDs is built largely on a self-certification procedure, placing heavy responsibility on manufacturers. Examples of current obligations include having in place a qualitative manufacturing process, user instructions that are clear and fit for purpose, ensuring that the 'physical' features of devices and diagnostics do not pose any danger such as electric shocks. If a product fulfils these and other related control requirements, it may be CE-marked as an indication that the product is compliant with EU legislation. The higher the risk associated with the use of a product, the stricter the obligation to perform clinical studies and to involve a so-called Notified Body to assess manufacturer compliance with the requirements [39].

The existing framework, which dates back to the 1990s, is currently under revision. If implemented, the EU Commission's recent proposal for a regulation on in vitro diagnostic medical devices (Proposal for a Regulation on in vitro Diagnostic Medical Devices) will change the way CDxs are regulated. With CDxs becoming one of the most important tools in achieving the goals of personalised medicine, it is an obvious shortcoming that they are not formally acknowledged within the current framework. Without a special distinction, they have to fulfil only minimal technical performance requirements and qualify for self-certification. This does not adequately recognise the impact a CDx has on a patient receiving the right treatment (or in avoiding the wrong treatment) [39].

The proposed IVD regulation addresses this gap. It provides a definition for CDx: 'a device specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy'. It also classifies IVDs into four risk categories. Based on high patient risk, coupled with a moderate public health risk, CDx will usually fall into class C – the second-high-

est risk class and requiring in-depth involvement of a notified body [15]. Both the specific identification and the change in classification are a step in the right direction. More rigorous review will help ensure the quality of CDxs, protect public health and promote the economic benefits of personalised medicine to the healthcare system. However, the definition should be improved to ensure that this unique class of IVDs, which plays an essential role in guiding treatment decisions with specific pharmaceuticals, is subject to a sufficiently high standard to guarantee patient safety [39].

Regarding the clinical evidence requirements, the proposal extends and clarifies the rules for clinical evidence ('the information that supports the scientific validity and performance for the use of a device as intended by the manufacturer') that IVDs have to follow, with requirements proportionate to the risk class. This is a welcome step to ensure that diagnostics undergo an adequate validation process. At the same time, the hurdles should not be so high as to make it nearly impossible to introduce a diagnostic tool. Diagnostics are different to pharmaceuticals, with shorter life cycles and a very different risk-benefit profile, explained by the fact that they do not interact directly with the patient's body; this means that they may merit different standards of clinical evidence in order to balance the risk-benefit profile and innovation. For instance, in the case of a new CDx, the report of the pivotal drug study should suffice to demonstrate both clinical performance ('the association of an analyte to a clinical condition or a physiological state') and scientific validity ('the ability of a device to yield results that are correlated with a particular clinical condition or a physiological state in accordance with the target population and intended user' [see 42]), without need for further scientific evidence [39].

Depending on the study design, scientific validity could be further augmented with information generated in earlier-phase drug studies or exploratory research. It should also be stated that such joint clinical trials of pharmaceutical and diagnostic are one, but not the only means of achieving the overall objective of clinical evidence.

For example, for follow-on diagnostics, where other manufacturers prepare a new IVD for an analyte that was previously included in an assessed and CE-marked CDx, a sufficiently robust clinical evidence report should still be required. Clinical evidence, however, might be appropriately demonstrated by means other than a full pivotal drug study, such as a retrospective analysis of clinically annotated archival samples [39].

Imaging Biomarkers

Going beyond the specific example of CDxs – and, in fact, beyond the scope of the IVD regulation – the case of imaging biomarkers may further serve to demonstrate the relevance of a regulatory framework which guarantees appropriate validation of medical devices and diagnostics. Medical imaging plays an important role in the era of personalised medicine, in particular in the areas of disease prevention, diagnosis, therapy, drug discovery, theranostics, image-guided interventions and drug delivery. Medical imaging has always been personalised, providing an individual phenotyping with the assessment of the location and severity of an abnormality. In the future, it will play an even more fundamental role in personalised medicine and should thus be considered an integral part of the entire 'omics' area. Using imaging biomarkers to streamline drug, tumour and disease progression discovery represents a clear advancement in healthcare. In order to allow an effective use of imaging biomarkers, adequate validation and standardisation procedures need to be in place. The qualification and technical validation of imaging biomarkers poses unique challenges in that the accuracy, methods, standardisations and reproducibility are strictly monitored. Moreover, there is a strong need to ensure full interoperability among the 'omics' biobanks, imaging databases and clinical data stored in electronic medical records [39].

Flexible Regulatory Process to Consider Different Diagnostic Models

The development and validation of new biomarkers is a priority in terms of improving patient management, assessing risk factors and disease prognosis. However, biomarkers that do not fit into a standard IVD model face regulatory challenges as many country laws restrict who can perform diagnostic tests and where they can be performed. These laws should evolve to focus more on the evidence supporting the use of the test and the quality of the testing methods. For example, most imaging biomarkers are not covered by the CE mark and do not currently fall under the EMA drug approval regulation. They are therefore unlikely to be covered by the EC directive on in vitro devices currently under development. In order to ensure their effective introduction of high-quality biomarkers, structured validation processes and evidence requirements need to be defined by EU and member state regulatory bodies [39].

Clinical Implementation and Reimbursement Pathways

Similarly to cancer drugs, recognising the clinical utility of value-based molecular diagnostics and the defini-

tion of the mechanism of reimbursement are required for an effective clinical implementation. This process requires usually two steps. First, there is a health technology assessment (HTA) by a regional or national agency, which evaluates the clinical utility of the molecular diagnostic; if the judgment is positive, a reimbursement recommendation is given. However, following this step, a commissioning decision is required which allows funding and payment of the molecular diagnostic. Currently, a number of European HTA bodies are developing dedicated pathways to assess molecular diagnostics. The National Institute for Health and Care Excellence (NICE) in the UK was one of the first agencies to set up a dedicated assessment pathway for diagnostics in 2009/2010 [40]. The aims of the NICE Diagnostics Assessment Programme (DAP) are to:

- Promote the rapid and consistent adoption of clinically innovative and cost-effective diagnostic technologies across the National Health Service (NHS)
- Improve treatment choice or the length and quality of life by evaluating diagnostic technologies that have the potential to improve key clinical decisions
- Promote the efficient use of NHS resources by evaluating diagnostic technologies that have the potential to improve systems and processes for the delivery of health and social care

This programme was unique in that it developed a specific methodology to assess diagnostic technologies, while other agencies have tried to assess diagnostics as part of their current framework. NICE evaluates diagnostic technologies based on 3 main categories: diagnostic test accuracy, clinical effectiveness and cost-effectiveness [41]. These categories align well with the areas of evidence that we have highlighted in this article for molecular diagnostics, which include analytical validation, clinical validation, clinical utility and cost-effectiveness [17, 39].

While NICE successfully established an assessment process for diagnostics, this process still has important limitations as diagnostic guidance is not legally binding in contrast to therapeutics and does not always specify a commissioning route. In other words, there is no obligation for the NHS to implement the NICE diagnostic guidance, and it is not always clear which budget stream will be utilised after NICE publishes its guidance.

Smaller countries such as Ireland, Switzerland and Belgium adopt a more pragmatic approach. Without creating specific assessment processes, they adapt their existing pathways to the requirements of molecular diagnostics and rely more on the advice from their clinical experts to inform their assessments. Assessing biomarkers re-

mains challenging for healthcare systems especially as the field is evolving and there is still uncertainty, especially around topics such as tumour heterogeneity, so these agencies need to base their decisions on the quality and quantity of evidence. Also, in many even after a positive health technology assessment, there are funding issues such as commissioning options and budget silos [39].

Therefore, new market access and validation models should be considered for healthcare systems which support reimbursement for molecular diagnostics [21]. After the molecular diagnostic is available as part of the healthcare system, molecular diagnostic developers should be expected to provide additional evidence on the clinical utility of the biomarker in different subgroups of patients. Implementing this type of market access scheme would greatly enhance the number of biomarkers being introduced, while also better defining in which clinical settings these tests have the most value to patients, physicians and the healthcare system. This approach, called 'conditional reimbursement', allows quicker access to validated molecular diagnostics in a controlled setting, allowing health authorities to assess the value and budget impact for the healthcare system before committing to broad access [39].

The Value-Based Pricing Approach

In most healthcare systems today, diagnostics are assigned a code and/or a price which is set based on the work required to perform the test, not based on the clinical value that the test provides to the healthcare system. If drugs were priced this way, pharmaceutical companies would only be reimbursed for the manufacturing costs of a product without taking into account the huge investment in research and development, and this approach would completely limit any innovation in the field. Similarly, a cost-based pricing approach for diagnostics disincentivises biomarker developers from pursuing evidence which demonstrates clinical value and limits their willingness to invest in further research [13]. An EU Commission Staff working document *Use of '-omics' Technologies in the Development of Personalised Medicine*, published in October 2013, highlighted this point: 'the current paradigm where the highest "value" is attributed to therapies rather than to diagnostics may need to be revisited to ensure that high-quality diagnostics are also valued appropriately. Such a shift would be expected to speed up innovation in the area of personalised medicine' [42]. Therefore, there is a need to shift the pricing of molecular diagnostics to a more value-based approach that rewards molecular diagnostic developers for (a)

demonstrating the value of their tests to healthcare systems and (b) sponsoring more research to be conducted [39].

Future Considerations

Based on rapid advances in sequencing and imaging technologies, a wide range of biomarkers are being developed and studied. Often, new biomarker models are being proposed that evaluate tumour, serum plasma or urine in a dynamic way along different steps of the patient's journey. Some of these new approaches require new evaluation methodologies to ensure that these markers are safe and effective in improving patient care. In some cases, alternative end points for studies will need to be considered to more efficiently introduce biomarkers into clinical practice. However, these options can only be considered once all known sources of bias are identified and appropriate controls established and caveats highlighted [39].

As cancer genomics sequencing becomes more widespread, it will be important to understand which oncogenic drivers may be actionable with different therapeutics and what evidence supports each target and its associated therapy [39].

Conclusions

One of the major barriers limiting the introduction of personalised cancer medicine is that there is a limited number of biomarkers developed and in clinical use today. Technologies like next-generation sequencing have great potential to enable better targeting of cancer drugs to those patients most likely to benefit. Currently, there are many large research initiatives to better characterise the underlying biology of cancer (The Cancer Genome Atlas, International Cancer Genome Consortium, etc.) which will lead to new discoveries and innovations in the development of biomarkers. While the field is still in its infancy and expected to become more complex, it is important that policy makers define clear frameworks for evaluation of biomarkers which are needed for regulatory approval and introduction into healthcare systems. By establishing clear pathways and evidence requirements, biomarker developers can better focus their research to meet these objectives.

Disclosure Statement

D.S. and J.P.-F. are employees of Genomic Health, of which they receive some stock.

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